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Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852

Division of Clinical Trial Design and Analysis
HFM-576

Memorandum

Date: December 6, 2000

From: Marc Walton, MD, PhD; OTRR/DCTDA MKW

Subject: Medical Officer Review of Response to CR Letter

Through: Karen Goldenthal, MD, Director, OVRR/DVRPA

BLA 99 - 1396
Response Submission to Complete Review Letter

Elan Pharmaceuticals

Botulinum Toxin Type B

For Treatment of Cervical Dystonia

Supplemental Clinical Review

OVERVIEW

Athena Neurosciences, Inc. submitted a marketing application, BLA 98-1396 on December 22, 1998 for botulinum toxin type B for use in the treatment of cervical dystonia. Athena was subsequently acquired by Elan Pharmaceuticals, Inc. All rights and ownership for the product transferred to Elan. The entire clinical development program of the product was conducted by Athena. In order to avoid confusion for future readers of this document, this review will refer to Elan as the developer, manufacturer, and marketer of the product, irrespective of whether or not study conduct or other events occurred prior to acquisition of Athena by Elan Pharmaceuticals.

Elan had initially proposed the trade name Neurobloc for the product. The proposed use of the product is in the treatment of cervical dystonia, with the proposed indication for labeling stated as: "NeuroBloc is indicated for the treatment of patients with cervical dystonia. ——— NeuroBloc treatment reduces the pain, ——— and severity of dystonia, ——— Note that the proprietary name has since been changed to "MYOBLOC". In this review, BotToxB will be used as an abbreviation for the product.

History of the BLA and Scope of this Review

The BLA clinical section contained a number of clinical study reports stemming from an extensive clinical development program occurring under ——— There were two open label still ongoing at the time of the initial BLA submission. Although open label, these two studies in fact form the bulk of the clinical experience with Botulinum Toxin Type B, and therefore are important subjects of review. While a safety update was submitted by Elan that contained extensive additional information on observations within these studies, this update was submitted at the end of the review clock cycle, and was unable to be included in the primary review. That clinical review concurred with Elan that substantial data supporting safety and efficacy was present, but there were extensive unresolved questions at the conclusion of that review. Consequently, a Complete Review Letter was issued requesting specific information to resolve the reaming issues. That letter was issued October 22, 1999.

That review document (dated October 1, 1999) should be consulted for extensive information regarding the disease, the product class, the overall clinical development program, and the specifics of study design and results. Information contained in that review document will largely not be repeated in this review, and assumed to be available and/or known to the reader of this document.

This review will be limited to the clinical data submitted by Elan in response to the Complete Review Letter sent by CBER to Elan. This information was submitted in several components, beginning with the document designated as Elan Amendment # 34, submitted January 12, 2000, and including Amendments # 35 (January 13, 2000), # 36 (January 19, 2000), # 37 (January 25, 2000), # 39 (February 14, 2000), # 42 (March 28, 2000), # 43 (April 10, 2000), # 45 (August 4, 2000), # 48 (November 13, 2000), # 49 (November 18, 2000) and # 51 (September 21, 2000).

This review will be organized according to the topic of information, rather than by the order of submission by Elan. The major issues raised in the CBER Complete Review Letter have been organized as follows:

1) Issues relating to generalization of the subject population or treatment regimen
   - Regarding use of BotToxB in subjects naïve to toxin of any serotype
   - Regarding the rationale and interpretation of exclusion of subjects with recent tetanus toxoid injection
   - A summarization of the characteristics of treatment administration
2) Issues relating to assessing the quality of the studies reported
3) Issues relating to the development of antibodies and neutralizing activity
4) Issues relating to potential relationship of specific AEs to dose or administration method
5) Request for updated and specific refinements in information on safety and efficacy
6) Issue of the change to NPF produced toxin,

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ISSUES RELATING TO GENERALIZATION OF SUBJECT POPULATION AND TREATMENT ADMINISTRATION

Clinical Experience in Toxin Naïve Subjects

In response to an inquiry, Elan has stated that all enrollment of subjects without any prior use of any serotype of Botulinum Toxin (i.e., neither Type A nor Type B) was limited to Study 351. As of the data cutoff for the response, September 1, 1999, there were only 9 subjects enrolled in Study 351 who had not had prior experience with a botulinum toxin for treatment of CD. All 9 had started at a dose of 5000 U, and 5 had progressed up to 15,000 U. At the lowest, and first dose (5000 U dose) there was a substantial rate of AE occurrence; 6 of 9 (67%) reported dry mouth, and 2 (22%) subjects reported 3 events of dysphagia.

Comment:

The vast majority of subjects studied in the Elan clinical database with BotToxB were in subjects who had prior experience with Type A toxin, and had subjectively had good responses. Implicitly, their perception of Risk-Benefit was that the adverse events were less concerning than the benefits were worth. Thus, there is potentially an element of self-selection, and enrichment in the Elan study subjects for patients who have had lesser adverse events and greater amounts of efficacy. The 9 subjects who were entirely toxin naïve are insufficient to draw any conclusions regarding the safety or efficacy in new CD patients. Potentially, the rates of adverse events, particularly those with sufficient severity to lead to discontinuation of toxin use, may be higher than seen in the Elan studies (the incidence rates for these 9 subjects were higher), or the rates or amount of benefit may be lower in newly diagnosed CD patients. There is no ability to address this uncertainty in the Elan dataset. This uncertainty should be directly acknowledged in product labeling.

Exclusion of Patients with Recent Administration of Tetanus Toxoid

All Elan studies excluded from enrollment subjects who had recently received Tetanus Toxoid. Elan states that was due to a concern for the toxoid to have raised antibodies which might have cross-reacted with BotToxB and thus shown up positive in the ELISA antibody assay. However, Elan states that there is no known neutralizing cross-reactivity of anti-Tetanus antibodies for protection from Botulinum. Thus, they believe there is not likely to be interference between tetanus immunization and use of BotToxB for treatment; but some theoretical potential for false positive ELISA assays for antibody formation. Elan notes that only 1 subject was turned away from enrollment in the studies due to this restriction.

Comment:

Tetanus toxoid immunization is widespread in the US population, so that it is likely there were many subjects with more distant history of immunization. Thus, persistent cross-reactive or neutralizing antibodies are unlikely since neutralizing antibodies were not observed in any study subject (although the initiating factor for the baseline ELISA positive results could be a persistent cross reactivity).. However, transient antibodies shortly following immunization has not been evaluated. The risk that there may be some cross-reactivity is not unreasonable, but since there is not an approved nor recommended test for BotToxB antibodies, the role for this concern in labeling, if any, is unclear. Since some reactivity against BotToxB appears in a minority of patients at baseline in these studies (see later section on immunogenicity) but does not seem to interfere with response, this matter does not seem to be critical information for labeling.

Characterization of the Treatment Administration During Studies

In the initial submission, Elan did not submit analyses that summarized the number of muscles injected in subjects, the relative frequency with which each specific muscle was utilized, and the relative dosing to various muscles. Elan now submits these dosing characterization summaries.

Study 009

In each treatment group, approximately 60% of subjects had 3 muscles employed, with the remainder of subjects evenly divided between use of 2 or 4 muscles.

Almost all subjects had the splenius capitus injected, with widespread (but not universal) injection of levator scapulae, sternocleidomastoid (SCM), and trapezius. The semispinalis capitus, and scalenus medius were injected with lower frequency.

The splenius capitus received about 50% of the total dose. When used, the levator scapulae received about 25% of the total dose, SCM 25%, trapezius approximately 30%. The semispinalis capitus received approximately 30% of the total dose, and the scalenus medius approximately 20%. No analyses were submitted to evaluate the dose used per specific muscle when 2 vs 3 vs 4 muscles were injected.

Study 301

In this study, approximately 90% of subjects received injections to 3 or 4 muscles, with only a small predominance of use of 3 muscles.

The great majority of subjects received injections to the splenius capitus (approx. 90%), with the sternocliedomastoid nearly as often (approx. 80% of subjects). The levator scapulae, trapezius, and semispinalis capitus were also frequently injected. The scalene muscles were rarely employed.

The splenius capitus received about 40% of the total dose, the SCM received approximately 20-25%. When used, the levator scapulae received about 20% of the total dose, trapezius approximately 30%. The semispinalis capitus received approximately 40% of the total dose. No analyses were submitted to evaluate the dose used per specific muscle when 2 vs 3 vs 4 muscles were injected.

Study 302

In the 10000 U active toxin group, 54% of subjects received injection to 3 muscles, the remaining 46% split nearly evenly between 2 and 4 muscles.

The great majority of subjects received injections to the splenius capitus (approx. 95%), with the sternocliedomastoid nearly as often (approx. 85% of subjects). The levator scapulae, trapezius, and semispinalis capitus were also frequently injected. The scalene muscles were infrequently employed (less than 20% of subjects).

Dose distribution was substantially similar to that of Study 301.

Study 352 and Study 351

These were the multiple treatment session studies. Most subjects received injections to 3 muscles, with the remainder largely split between 2 and 4 muscles. A small fraction of the treatments employed 5 muscles.

The utilization rates and dosing of specific muscles is largely similar to that of Studies 301 and 302.

Comment:

A summary of this information should be placed in the labeling to guide physicians as to the dose distribution that has been evaluated. There were no explicit guidelines to investigators on which muscles to use, or how to divide the doses, so that this information is likely dependent upon the specific investigators who conducted these studies, and their subjective impressions of what muscles are most important in this condition and of the relative sensitivity of these muscles to toxin. Their pre-existing biases would have been formulated during their experience in clinical practice with off-label used of Botulinum Toxin Type A. While the pattern of administration observed in these studies is thus not one developed and optimized through rigorous scientific investigation with this product, it is reflective of the way the product is likely to be used in general clinical practice.

Labeling should provide a description of the relative rates of total number of muscles injected per session, which muscles were used, and the typical range of doses per specific muscle. Consideration should be given for this last that it may be preferable to express as percent of the total session dose and eliminate apparent implicit recommendation of specific total units per session.

Dosing Characterized as Fraction of Total Dose

In response to an additional request, Elan submitted information on dosing in each muscle characterized as percent of total dose administered to the subject. This permits comparison between dose levels, as it eliminates differences based simply on actual units, and permits comparison of placebo "dosing" to the toxin groups as well. For studies 301 and 302 the results submitted were as follows.

Table 1: Summary of Treatment of Muscles in Phase 3 Studies as Percent of Subjects

		Study 301			Study 302		Averages	
		Placebo n = 36	5000 U n = 36	10000 U n = 37	Placebo n = 38	10000 U n = 39	All Groups	Toxin Only
Number of Muscles Injected	2	8	19	13	18	23	16	18
	3	44	42	49	39	54	46	48
	4	47	39	38	39	23	37	33
Utilization Rate By Specific Muscle	Splenius Capitus	94	89	81	95	95	91	88
	Sternocleidomastoid	89	81	76	87	85	84	81
	Semispinalis Capitus	58	50	57	55	49	54	52
	Levator Scapulae	53	44	65	32	31	45	47
	Trapezius	36	44	43	29	26	36	38
	Scalenus Ant.	8	11	3	26	13	12	9

Note: The Averages columns are crude averages of the listed columns, not calculated from original data, and for general comparison only

Note: Values shown are percentage of subjects for each row's characterization

Table 2: Summary of Treatment Administration in Phase 3 Studies as Percent of Total Dose

		Study 301			Study 302		Averages	
		Placebo n = 36	5000 U n = 36	10000 U n = 37	Placebo n = 38	10000 U n = 39	All Groups	Toxin Only
Splenius Capitus	25th Pctle	25	30	25	30	35	29.0	30.0
	Mean	28.2	43.5	36.4	44.8	43.7	39.3	41.2
	75th Pctle	50	57.5	45	52	50	50.9	50.8
Sternocleidomastoid	25th Pctle	20	15	20	20	20	19.0	18.3
	Mean	23.7	20	26.5	24.5	30.2	25.0	25.6
	75th Pctle	25	25	30	30	37.5	29.5	30.8
Semispinalis Capitus	25th Pctle	25	30	30	20	25	26.0	28.3
	Mean	35.6	43.8	43	25.2	32.6	36.0	39.8
	75th Pctle	50	60	50	30	40	46.0	50.0
Levator Scapulae	25th Pctle	15	13.8	11.3	18.8	15	14.8	13.4
	Mean	18.9	17.8	18.3	25	18.5	19.7	18.2
	75th Pctle	20	20	20	27.5	20	21.5	20.0
Trapezius	25th Pctle	15	20	22.5	20	20	19.5	20.8
	Mean	28.5	28.8	31.6	21.6	24.8	27.1	28.4
	75th Pctle	35	35	42.5	25	33	34.1	36.8
Scalenus Ant.	25th Pctle	20	15	20	20	22.2	19.4	19.1
	Mean	21.7	23.8	20	26.1	28.2	24.0	24.0
	75th Pctle	25	32.5	20	30	33.5	28.2	28.7

Note: The Averages columns are crude averages of the listed columns, not calculated from original data, and for general comparison only

Note: Values shown are percentage of total dose administered to subject (volume for placebo subjects)

Comment:

These tables provide a manner of presenting the dosing in the phase 3 studies that is not explicit regarding the actual total dose administered. This can be viewed as generalized information that can be applied to any specific dose. The dosing between groups within a study and between these two studies was fairly consistent when viewed in this manner. Elan was requested to employ the pooled toxin group data for use in labeling.

FOLLOW-UP INFORMATION REGARDING THE QUALITY OF CONDUCT OF REPORTED STUDIES

Comparison of Intended Dose to Actual Received Dose

Elan has submitted analyses that indicates that for all the studies conducted by Elan, the actual received dose is nearly the same as the intended dose. There were relatively few subjects who did not received nearly all of the assigned dose.

Evaluation Schedule Compliance

The Week 4 evaluation was the primary endpoint time-point for the controlled studies. Only summaries for this most critical evaluation were submitted. For studies 009, 301, and 302, Elan reports that for the Week 4 evaluation the great majority of subject evaluations were within the ±3 days window specified by the protocol. Few subjects were outside this window, the worst case Study 301 where 10% did not meet the study plan. However, nearly all subjects were within 7 days of exactly 4 weeks (i.e., evaluation occurred at 3 to 5 weeks post injection). Only rare subjects in these studies were greater than 7 days off in evaluation.

In Study 352 compliance within 3 days occurred for approximately 77% of planned visits, and 93% were within 7 days. There were approximately 3% of visits that never occurred (missing data).

In Study 351 approximately 70% of planned Week 4 visits occurred within 3 days, 90% within 7 days, and 95% within 14 days. There was general consistency in these percentages across treatment cycles.

Comment:

This appears to be adequate compliance with the evaluation schedule to accept the study results as interpretable per study expectations. The effect of the toxin does rapidly wax or wane over the period of week 3 to 5.

Amounts of Missing Data

Elan submitted a summarization of the amounts of missing data in Studies 009, 301, 302, 352 and 351. There was no missing baseline evaluations. Week 4 evaluations were present in the great majority of subjects; Study 009 had none missing, Study 301 and 302 each had only 1 subject missing Week 4. Study 352 has small amounts of missing evaluations, but some of these may be due to dropout of subjects from the study, and not solely subjects who received an injection and failed to return for a Week 4 evaluation. Study 351 has 3 to 6% of subjects with missing Week 4 evaluations in the latter cycles of the study. Week 8 evaluations were also nearly all present in Studies 301 and 302.

Procedure for Measurement of VAS Tools

Elan submitted information that described the method of measurement used for the several VAS tools in the studies. CRF pages completed at the study site were transferred the CRO for the study, where CRO staff made the measurements in a standardized manner, and using a standardized ruler. This measurement was confirmed by a CRO coordinator staff member. Discrepancies were jointly resolved.

Comment on All Above Subsections:

These four answers adequately allay any concerns regarding potential serious study flaws in these areas. The study doses can be regarded as the planned dose, the evaluations were not unfairly biased in timing, the majority of the data was properly observed, and the VAS tools were read without bias and in an adequately reliable manner.

FINAL STUDY REPORT FOR STUDY 352

Study 352 completed after the submission of the original BLA, and a final report for the study is submitted in these BLA amendments.

DESIGN

Study design was fully presented in the October 1, 1999 Clinical Review document. No protocol modifications were made after study initiation. The prior review document should be consulted regarding a full description of study design. This was an open label, intra-subject dose escalation study. Briefly, CD subjects with a history of prior use of Botulinum Toxin Type A with perceived benefit were enrolled, and underwent 3 cycles of injection session with clinical follow-up. After a treatment session, follow-up was every 4 weeks, and when a subject returned to their pre-injection baseline, they were eligible for the next cycle injection. Subjects sequentially received 10000 U, 12500 U, 15000 U in the three sessions. An inability to escalate the dose further would result in termination of the subject's study participation, rather than injection with a dose not of the planned escalation program.

STUDY PERFORMANCE AND SUBJECT CHARACTERISTICS

The study was initiated in June 1997, and completed March 1999. There were 16 study sites, mostly in North America (11 US, 1 Canada, 4 UK).

There were 145 subjects enrolled, of which 136 continued into cycle 2 (9 withdrawals), and 125 continued into cycle 3 (11 withdrawals). Early withdrawals were 13 for adverse events, 4 for "patient request", 2 for non-compliance, and for a "sponsor decision" and 6 for "other" reasons. Adverse event withdrawals occurred 6 prior to entry to cycle 2, 6 additional prior to entry to cycle 3, and 1 after the cycle 3 injection. Of these, 1 withdrawal was due development of Non-Hodgkin's lymphoma, later followed by death.

Withdrawals for "patient request" were 3 for preference for BOTOX treatment, and 1 for financial reasons. The 6 withdrawal's for "other" reasons included 4 for perceived lack of efficacy, 1 for moving to another state and travel impracticalities, and 1 for travel impracticalities due to subject becoming incarcerated.

There were 3 minor protocol eligibility deviations that do not impact the study interpretation. There were 11 cases of a subinvestigator performing study procedures that the protocol called for the principle investigator to perform. There were 22 cases of more than the permitted maximum 5 injection sites within a single muscle being used. There were 65 cases of an incomplete or absent study visit, and 194 cases of a visit not entirely within the planned scheduling window.

Demographics of the final enrolled population were similar to the interim report (when 136 of the final 145 subjects were enrolled). Mean age was 53 years, 65% of subjects were female, 95% Caucasian, and mean weight was 73 kg. 78% were considered Type A toxin responsive at enrollment (22% considered secondary Type A unresponsive after an initial period of responsive).

Treatment characteristics have been described previously in this review document.

RESULTS: DYSTONIA STATUS ASSESSMENTS ON STUDY

Complete results for the study were presented by Elan, including several exploratory analyses requested by CBER.

Table 3: Dystonia Assessment Results in Study 352

Assessment	Time Point	10000 U Cycle n= 145 injected	12500 U Cycle n= 136 injected	15000 U Cycle n= 125 injected
TWSTRS Total	Cycle Baseline	47.2	47	46.9
	Week 2	38.3	37.3	37.5
	Week 4	37.6	37	36.4
	Week 4 Improvement	9.6	10	10.6
	Week 8	41.8 (n=141)	40.1 (n=133)	39.0 (n=122)
	Week 12	44.0 (n=102)	43.2 (n=97)	42.6 (n=110)
Patient Global VAS	Week 4	57.8	61.1	61.6
	Week 8	49.2	52.6	57.3
Investigator Global VAS	Week 4	64.0	64.9	65.2
	Week 8	56.0	58.7	62.5
Patient Pain VAS	Cycle Baseline	39.0	37.6	38.0
	Week 4	60.2	63.0	61.4
	Week 8	48.2	51.3	57.7
	Week 4 Improvement	21.1	25.4	23.4
	Week 8 Improvement	9.7	13.8	20.2
Percentage with at least 20% TWSTRS Improvement	Week 4	49%	52%	46%
TWSTRS Severity Subscale	Cycle Baseline	20.0	19.8	19.8
	Week 4	16.6	16.0	15.8
TWSTRS Disability Subscale	Cycle Baseline	15.6	15.9	15.8
	Week 4	13.1	13.1	12.8
TWSTRS Pain Subscale	Cycle Baseline	11.6	11.3	11.4
	Week 4	7.9	7.9	7.7

Note drop in numbers of subjects assessed at Week 8 and later, due to transition of subjects into next cycle

Note that approx 1/4 of cycle 2, and majority of cycle 3 Wk 4 assessments obtained after interim data

CBER requested supplemental analyses that examined Dystonia Assessments across cycles in the same set of patients. Elan submitted an analysis of the amount of improvement from baseline for the 125 subjects who participated in all three cycles.

Table 4: TWSTRS Change in Subjects Who Participated in All 3 Cycles

		10000 U Cycle Same 125 subjects subset all 3 Cycles	12500 U Cycle Same 125 subjects subset all 3 Cycles	15000 U Cycle Same 125 subjects subset all 3 Cycles
TWSTRS Total	Baseline	47.4	46.9	46.9
	Week 2 Improvement	9.2	9.4	9.4
	Week 4 Improvement	9.9	9.8	10.6

Analyses for other variables were not submitted. Analyses were provided of change in TWSTRS for Week 8 and Week 12 assessments, but the numbers of subjects who had these evaluations in all three cycles was progressively fewer, and these analyses did not provide any indications different than that shown above. Per a CBER request, an analysis of subjects who participated in at least Cycles 1 & 2 was also submitted:

Table 5: TWSTRS Outcome in Subjects Who Participated in 2 Cycles

		10000 U Cycle n= 136	12500 U Cycle n= 136	15000 U Cycle n= 125
TWSTRS Total	Baseline	47.5	47.0	46.9
	Week 4	37.3	37.0	36.4
	Week 4 Improvement	10.2	10.0	10.5

Comment:

There is no evidence in these analyses that the higher dose amounts provided any additional efficacy over the 10000 U dose. This is in spite of the open label nature of this study, with known dose escalation, which may have provided a bias in expectation of greater efficacy in successive cycles.

Cycle duration was not fixed, but dependent on the scheduled visits and the perceived state of the subject as retaining benefit or having returned to cycle start baseline. The mean duration of cycles were 12.1 weeks Cycle 1, 12.9 weeks Cycle 2, and 13.9 weeks Cycle 3.

Comment:

Differences in Cycle duration cannot easily be interpreted. While the design would allow for earlier loss of effect to be reflected in cycle duration, this was an open label design with doses escalated in a known fixed manner for all subjects. It is not possible to distinguish the relative contributions of a) higher dose, b) the open label potential bias of expectation of longer duration with higher dose, and c) accumulation of effect over successive treatment cycles to the longer duration treatment cycles. At best, 50% higher dose contributed to lengthening cycle length by 1.8 weeks (15% longer). This remains a only a weakly suggested finding, however.

SAFETY RESULTS

Deaths, Serious Adverse Events, and Withdrawals due to AE

There was one death, due to non-Hodgkin's lymphoma. Serious AEs totaled 10 in 9 subjects. There were 3 in Cycle 1, 4 in Cycle 2, and 3 in Cycle 3. The additional SAEs (beyond the death) consisted of cholelithiasis, a GI carcinoma, renal calculus, calf cellulitis, varicose veins with vein striping, sarcoidosis with peptic ulcer, psychotic depression, and gastroenteritis.

There were 13 subjects who withdrew due to AEs. 6 during cycle 1, 6 during Cycle 2, and 1 during Cycle 3. The causes included 1 psychotic depression, 6 with dysphagia (of which 4 also had dry mouth), 1 with dry mouth, 1 with dry mouth and neck pain, 1 with worsening of CD, and 1 each with dyspepsia with esophagitis, herpes zoster; and non-Hodgkin's lymphoma.

Adverse Events in General

The adverse events occurring most frequently during this study were similar to those reported in the interim analysis, and observed in the other studies.

Table 6: Percent Incidence of Frequent AE in Study 352 by Dose Cycle (at least 10% in one dose cycle)

AE	10000 U cycle n = 145	12500 U cycle n = 136	15000 U cycle n = 125
Infection (unspecified)	11	14	10
Injection site pain	17	15	6
Dysphagia	37	40	21
Dyspepsia	17	9	7
Dry Mouth	54	43	34
CD related Neck Pain	10	11	11

Note: 8 additional AE types occur for limit of 5%

Most events were of mild intensity, only rare events were severe:

Table 7: Distribution of Percentage Incidence for Selected Adverse Events Separated by AE Severity Grade

AE	Severity	10000 U cycle	12500 U cycle	15000 U cycle
Dysphagia	Mild	25	25	14
	Moderate	10	13	3
	Severe	1	2	3
Dry Mouth	Mild	37	27	26
	Moderate	16	15	8
	Severe	2	1	0
Dyspepsia	Mild	9	4	3
	Moderate	6	5	3
	Severe	2	1	3

The adverse event of dysphagia occurred in a total of 79 subjects in at least 1 Cycle; 38 in only 1 Cycle, 28 in two Cycles, and 13 in all three Cycles. Almost all subjects who had dysphagia only once experienced it in the first or second Cycle. Approximately 2/3 of subjects who had dysphagia in Cycle 1 either also experienced dysphagia in Cycle 2 or did not participate in Cycle 2 due to adverse events.

There were some but few subjects with dysphagia graded as severe. The fraction of dysphagia graded as severe dysphagia increased in successive cycles. No therapeutic interventions were recorded as employed for these subjects in response to the dysphagia. Changes in diet or other habits, if any, were not recorded.

Comment:

The decrease in AE rates across the sequence of cycles is noticeable, but not readily attributable. The decrease could possibly be related to the drop out of subjects with a propensity for AEs, or due to investigators changing the injection method for the subjects over

the 3 cycles to minimize the AE occurrence (as the investigators learned what each subject was sensitive to), or for subjects becoming more expecting of the same AE, leading to toleration, and thereby reporting it less often, or for a combination of these mechanisms. As there is no ability to distinguish between these or some other effect, the AE rates of the latter cycles are not reliable predictors of the AE rates in these subjects over that observed in the first injection session.

Antibody Formation Results

The report of antibody formation for Study 352 was written in a separate Study Report, dated 1/6/2000. The limit of detection for the quantitative ELISA was 5 units/ml, and this became the definition of a positive result. Cross reactivity with anti-tetanus antibodies with this assay was observed.

The Mouse Neutralization Assay (MNA) was performed on samples with a positive ELISA. The MNA assay employed 4 mice per sample, with a positive neutralization test defined as survival of 3 or 4 of the 4 mice at a specific dilution (survival of only 2 was not regarded as indicating neutralization).

In Study 352, samples for ELISA were collected at screening, at the start of each subsequent Cycle, and at study termination. All subjects had samples according to participation, however 6 samples contained too little volume to be feasible to analyze.

Of the 145 subjects, 43 (30%) had a positive ELISA at least once during the study. There were 21 positive at screening, 24 at end of cycle 1, 21 positive at end of cycle 2, and 29 positive at end of Cycle 3. There were also 5 subjects with positive ELISA at an early termination visit.

Of these subjects there were 17 subjects (12%) who had a negative screen ELISA, and positive at end of study. Most subjects who entered the study with a positive screen ELISA remained positive at study end; only 3 subjects became ELISA negative during the study. There were also three subjects who became newly and only transiently positive during the study, and 2 subjects who had no screening ELISA but were positive at end of study, and may be new ELISA positive as well.

MNA results were that only 4 subjects developed a positive MNA. All 4 subjects were amongst those who had an on-study positive ELISA with a negative screening ELISA (20%). There were no equivocal MNA results (e.g. 2 of 4 animals surviving). All assay results either 0, 1, 3, or 4 animals surviving IP toxin challenge. Of these 4, 2 discontinued due to perceived lack of efficacy, and 2 continued in the study.

Comment:

There was a substantial rate of baseline positive ELISA (approximately 14.5%), but also a substantial development of new sustained positive ELISA tests with 3 cycles of BotToxB (12%). Of the new ELISA positive subjects, 20% became MNA positive, for an overall rate of MNA positive of approximately 2.8% over 3 treatment cycles.. If this amounts to ¾ of a year, then a MNA rate of 3.7% per year is suggested. However, that is not a strong prediction, as it is possible that the subjects with a propensity to develop neutralizing antibodies all did so, and that the remaining subjects would not do so.

DEVELOPMENT OF ANTI-TOXIN ANTIBODIES AND NEUTRALIZING ACTIVITY

INDIVIDUAL STUDY SUMMARIES

Study 009

There were no positive ELISA results, either at screening or end of study. There was 1 subject missing from testing in each group. Only few MNAs were performed, none positive.

Study 301

Baseline ELISA was performed on 103 samples, with 11 (11%) positive. There was 1 new positive ELISA in the combined BotToxB subjects (1 of 69) but also 1 new positive ELISA in the placebo group (1 of 32). There was no positive MNA on any of the ELISA positive samples tested.

Study 302

There were 77 samples tested at baseline, with 8 positive (10%). There were no new positive ELISAs in the BotToxB group, but one new positive ELISA in the placebo group (1 of 37). None of the few MNAs done were positive.

Study 352

These results were described more fully in the summary of the Final Study Report of this open label, uncontrolled study. There were 136 samples tested at baseline, with 21 positive (15%). There were 136 samples tested at subject termination, with 35 positive (17 new positive in 124 non-baseline-positive subjects, 14%). Most baseline ELISA positive subjects remained positive at study end. There were 4 positive MNA results, all in the subjects who were ELISA negative at baseline and developed positive ELISA on study.

Supplemental information in Amd 51 indicated that unlike the observations in Study 301 and 302, there were some subjects who did develop new ELISA positive assays after a single treatment session (7 subjects).

Study 351

Revised tables of results were requested from Elan and indicate that approximately 15% of subjects were ELISA positive at baseline. Through a total of 4 treatment sessions, the baseline plus new positive subjects reached approximately 41% ELISA positive. There were successively fewer subjects with more than 4 treatment sessions complete included in the analysis. Although additional subjects continue to develop new ELISA positive results, estimating percentages becomes problematic in this simplistic analysis. MNA results of Study 351 are difficult to interpret in isolation as many subjects rolled over from prior studies with varying amounts and numbers of toxin treatments.

Comment:

It is noteworthy that Studies 302, 302, 352 and 351 all suggest baseline ELISA positive rates of 10 to 15% in these subjects, all who have a history of Type A Botulinum Toxin use. Many of these subjects will also have had a history of tetanus toxoid immunization as well. The single treatment session studies of 009, 301, 302 do not suggest a significant rate of ELISA positive conversion, although Study 352 does indicate that some subjects may convert after a single treatment session with 10000 U. However the multiple treatment session study 352 does suggest there is substantial conversion (14%) over the course of 3 treatment sessions, and this is further supported by the ELISA results of Study 351.

POOLED STUDIES 301, 302, 352, 351 ANALYSIS

There were 468 subjects included in this pooling of studies. Of these, 57 of 446 (12.2%) were ELISA positive at baseline. By the end of session 4, of those 324 subjects tested (excludes those not reaching 4 completed sessions by the data cutoff date as well as 8 missing subjects and 19 previously discontinued subjects) 90 (27.1%) were positive. However some of the excluded subjects were known to be ELISA positive, so this figure presents only a minimum. This analysis also indicates that of 441 subjects tested at the end of Cycle 1, 21 new ELISA positives were found (4.8%). The analysis table included time since first toxin treatment and total cumulative dose received for the subjects separated by ELISA status. These tables did not indicate these factors were able to distinguish the ELISA positive vs negative subjects to any notable degree.

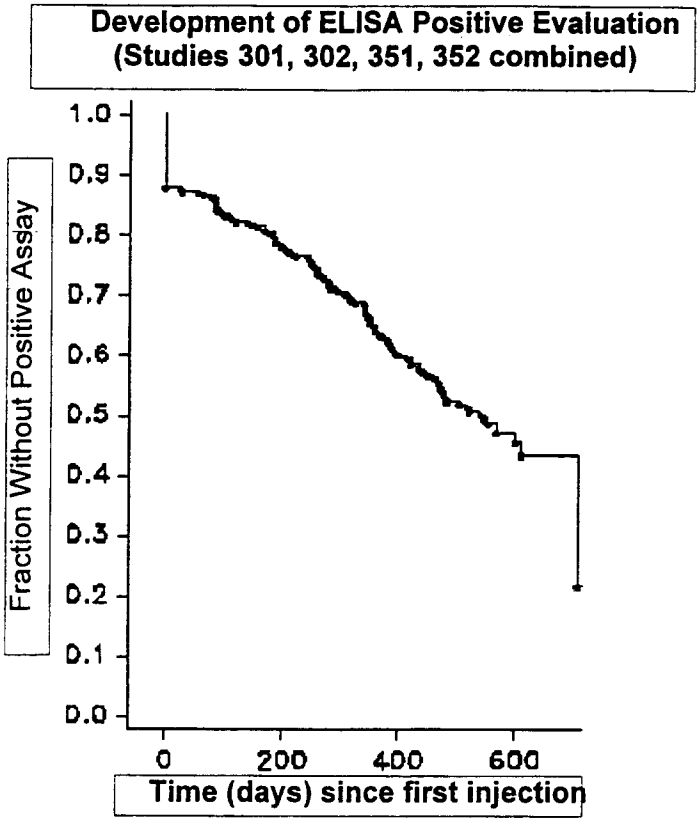
Pooled results for MNA testing confirmed that subjects were progressively converting to MNA status over the course of these studies. However, since relatively few subjects were tested at any time (related to being ELISA positive and when the sample fell within the MNA performance cycles) the MNA results are difficult to interpret in this analysis.

In order to address the difficulty of varying duration of participation of subjects, and of not testing all ELISA positive samples for MNA (only the last sample for each subject with a positive ELISA within the assay performance cycle was tested for MNA) a Kaplan-Meier type of analysis was performed on the pooled dataset. For this analysis, the event was deemed to be either development of ELISA positive assay result or MNA positive assay result, time to event was the time from first toxin injection (and defined to be a value of 0 for those subjects who were positive at baseline). For the MNA analysis, due to the fact that only the last available sample was tested, time to MNA positive was imputed to be time to first positive ELISA without known negative MNA (i.e., for those subjects who did eventually develop a positive MNA, the subject was treated as if it occurred at the same time as the ELISA became positive if no data to contradict this was available).

For the ELISA analysis, there were 467 subjects included in the analysis, of whom 195 developed a positive ELISA at some time, for a gross overall rate of 42%. However, since there was varying amounts of time until censoring, the K-M plot reveals over 50% of subjects develop a positive ELISA within 2 years of repeated treatment cycles. The median time to positive was 541 days overall (see Figure 1). Excluding those subjects ELISA positive at baseline, 138 became newly ELISA positive, with a median time to positive of 610 days.

In detail, 12.2% were positive at baseline, 20% positive at 6 months, 36.1% positive at 1 year, 50% positive at 18 months. At 610 days there were 56.7% ELISA positive, with no substantial amount of data beyond that time. This suggests approximately a 12% rate of conversion per 6 months of repeated use of toxin.

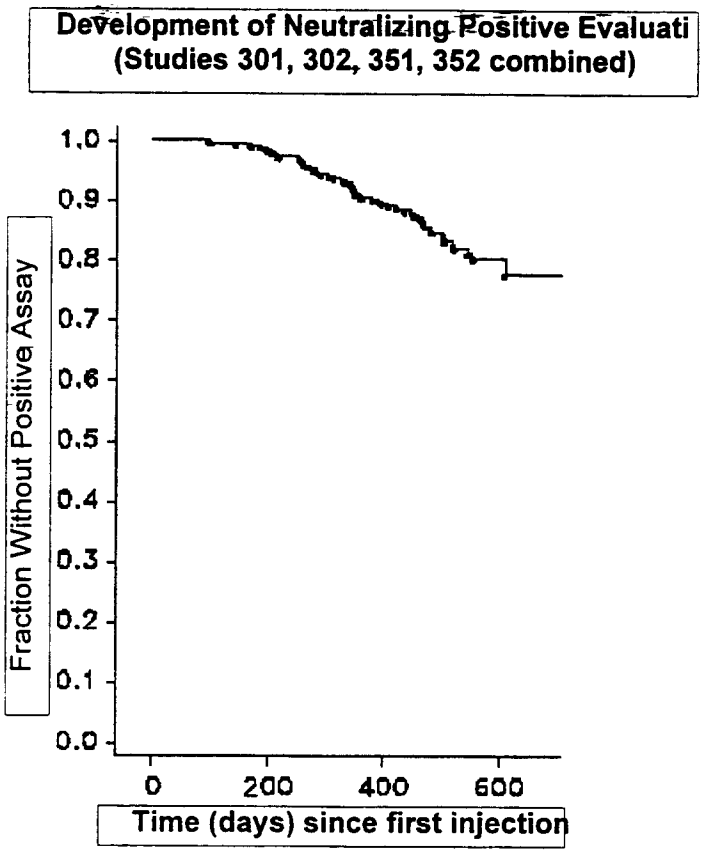
Figure 1



An analysis of subjects separated by those who discontinued (the minority) vs those who did not, suggested an earlier development of ELISA positive status in those who discontinued. However, the overall rates were not substantially different, and ELISA positive does not appear to be a dominating influence on discontinuation. An analysis of time to discontinuation after becoming ELISA positive was not performed, but is not likely to be informative.

For the MNA analysis, there were 460 subjects included, of whom 57 developed a positive MNA at some time (12.4% overall). As 50% MNA positive did not occur, no median time to MNA positive could be calculated. However, at 1 year 9.6% of subjects were estimated as MNA positive, 18.2% at 18 months, and the analysis suggests 22.6% MNA positive at 610 days. There were no notable numbers of subjects MNA positive until after 6 months in the analysis, which suggests that approximately 9% become positive per 6 months of toxin use thereafter.

Figure 2



While analyses of continuation status did not show that ELISA positive nor MNA positive had a dominating influence on continuation or discontinuation status, there were greater percentages of positive subjects among those that discontinued than those that did not, suggesting that there is some impact of antibody positive conversion.

There was no attempt to correlate either ELISA positive or MNA positive status with clinical response in these analyses. However, most of the subject time in the analyses was on uncontrolled studies, so there is little ability to perform such an assessment.

Comment:

These results indicate that there is substantial formation of antibodies in response to treatment with Botulinum Toxin Type B, and that many patients will convert to having neutralizing antibodies within 2 years of beginning treatment. No analyses were able to establish factors which significantly influence the rate of antibody formation. However some analyses suggest that these responses may have an impact on the patient's decisions to continue using the toxin. Of important note, there were not any notable anaphylaxis or other hypersensitivity reactions noted with this immune response development. Thus, to date this does not appear to be a notable safety risk.

Nonetheless, this information warrants placing in the product labeling. Additionally, since the data on actual rates were relatively weak in these analyses, further information from post marketing studies is warranted.

POTENTIAL RELATIONSHIP OF ADVERSE EVENTS AND ADMINISTRATION CHARACTERISTICS

In response to request, Elan submitted additional analyses using logistic regression exploring the data for relationships between dose in specific muscles and incidence of specific adverse events. Because of their frequency and potential importance, including cause for subject decisions to discontinue treatments, Dry Mouth and Dysphagia were employed for analysis. The meta-analysis of Studies 009, 301 and 302 combined were the most informative for this. Dry mouth has an association of increased frequency with increased dose administered to the muscles Splenius capitus, trapezius, and sternocleidomastoid. Dysphagia has a notable relationship of incidence only with dose administered to the sternocleidomastoid.

As previously seen in the single AE / muscle relationship analysis submitted in the original BLA submission, the confidence interval around frequency is broad, but shows substantial frequency (50 to 70% of subjects) in the central tendency estimate at the higher end of actual doses administered.

Comment

These analyses should be recognized in the product labeling. The estimates of actual frequency with dose are too broad in confidence interval to be appropriate for readily interpretable labeling, but the existence of a relationship should be described for the specific muscles. There were too few of the more severe grades of these AEs to allow informative analyses of a dose - severity relationship.

UPDATED SAFETY AND EFFICACY RESULTS AND ADDITONAL EXPLANATORY ANALYSES

STUDY 352

The final Study Report for Study 352 was submitted and reviewed previously in this document.

STUDY 351

Study 351 served as the open label extended treatment safety study for all subjects as their participation in a prior study completed. See the October 1999 Clinical Review for a full description of study design. Study 351 was further modified beyond that description to allow for a limited number of study sites to escalate subjects up to a maximum dose of 25000 U of toxin, via steps of 2500 or 5000 U. An additional addendum planned for the exploratory development of a F-TBT tests, analogous to the F-TAT test for insensitivity to Botulinum Toxin Type A, but instead to assess for resistance to Type B toxin. The Addendum would enroll subjects in a cohort manner to determine a minimum dose of BotToxB that produced complete inability to wrinkle the forehead. The findings on the F-TBT development were not submitted to the BLA.

Efficacy Assessment Outcomes

Updated summary analyses of Study 351 outcome assessments by Treatment Session, and by Session Dose were submitted.

Table 8: TWSTRS Outcome in Study 351 by Treatment Session

Session #	1	2	3	4	5	6	7
n	419	378	346	303	249	179	93
Baseline TWSTRS	47.5	45.6	44.3	44.6	45.4	44.7	44.2
Week 4 TWSTRS	36.3	36.6	36.6	37.9	38.4	39.1	40.3
TWSTRS Improvement	11.2	9.0	7.7	6.7	7.0	2.6	3.9

Number of patients in treatment session shown as n

Table 9: CD Outcome in Study 351 by Dose Range Groups

	Dose	<= 5000 U	>5000 U to < 10000 U	10000 U to < 12500 U	12500 U to < 15000 U	15000 U to < 17500 U	17500 U to < 20000 U	=> 20000 U
TWSTRS	n	62	39	506	400	800	84	101
	Baseline	44.6	40	44.5	44.5	45.8	47.6	50.9
	Week 4	34.2	31.1	33.8	36.2	39.1	42.8	46.2
	Change	10.4	8.9	10.7	8.3	6.7	4.8	4.7
Patient Global	n	62	39	505	400	799	84	101
	Week 4	63.1	72.1	67.0	65.2	62.0	56.4	55.3
Patient Pain VAS	n	62	39	507	400	800	84	101
	Baseline	40.6	50.5	40.5	45.3	41.5	38.5	33.2
	Week 4	62.8	68.6	65.4	63.6	59.4	52.7	51.3
	Change	22.2	18.1	24.9	18.3	17.9	14.2	18.1

Note that n is number of treatment sessions; number of unique subjects is smaller

Comment:

These two tables suggest that there may be a lessening of treatment benefit with succeeding treatment sessions (Table xx) and/ or a lessening of treatment benefit with the uppermost levels of dosing examined. However, these interpretations are not definitively supported. These sequential dosing sessions include different subsets of subjects, and the dose level analysis includes both different subsets of subjects and different numbers of treatment sessions within each column. Thus no definitive conclusions may be drawn from comparisons between columns.

Per CBER request, results were also submitted in subject subsets consisting of the same subjects with multiple treatment sessions. The following table shows the CD outcome assessment and incidence of dysphagia and dry mouth in these subsets. Also shown in each row are the results for the following treatment session for the subset of subjects who went on to a subsequent session.

Table 10: Subsets of Same Subjects with Mulitple Sessions							
		Session Number					
		1	2	3	4	5	6
Number in Subset		377	378	346			
TWSTRS	Baseline	47.5	45.6	44.6			
	Week 4	35.9	36.6	36.6			
	Improvement	11.6	9.0	8.0			
Patient Global Assessment		65.7	65.1	65.0			
Pain VAS	Baseline	37.9	40.8	43.4			
	Week 4	64.6	62.7	62.8			
	Improvement	26.7	21.9	19.4			
Dysphagia	%	20	11	10			
Dry Mouth	%	32	21	12			
Number in Subset		346	346	346	303		
TWSTRS	Baseline	47.4	45.3	44.3	44.6		
	Week 4	35.3	36.1	36.6	37.9		
	Improvement	12.1	9.2	7.7	6.7		
Patient Global Assessment		66.9	66.5	65.0	62.6		
Pain VAS	Baseline	38.0	41.1	43.4	43.3		
	Week 4	65.7	63.5	62.8	60.4		
	Improvement	27.7	22.4	19.4	17.1		
Dysphagia	%	19	11	10	5		
Dry Mouth	%	33	21	12	6		
Number in Subset		303	303	303	303	249	
TWSTRS	Baseline	47.5	45.3	44.2	44.6	45.4	
	Week 4	35.7	36.0	36.3	37.9	38.4	
	Improvement	11.8	9.3	7.9	6.7	7.0	
Patient Global Assessment		66.8	67.2	65.9	62.6	61.7	
Pain VAS	Baseline	37.5	41.2	44.0	43.3	40.7	
	Week 4	65.4	63.0	63.3	60.4	59.5	
	Improvement	27.9	21.8	19.3	17.1	18.8	
Dysphagia	%	17	11	10	5	7	
Dry Mouth	%	33	22	13	6	7	
Number in Subset		249	249	249	249	249	179
TWSTRS	Baseline	47.8	45.4	44.1	44.4	45.4	44.7
	Week 4	36.0	36.2	36.0	37.8	38.4	39.1
	Improvement	11.8	9.2	8.1	6.6	7.0	5.6
Patient Global Assessment		65.5	67.1	66.7	63.0	61.7	61.5
Pain VAS	Baseline	35.9	40.6	43.5	43.5	40.7	44.9
	Week 4	64.0	62.1	63.5	61.0	59.5	58.0
	Improvement	28.1	21.5	20.0	17.5	18.8	13.1
Dysphagia	%	16	12	11	5	7	4
Dry Mouth	%	35	25	14	7	7	6

Comment:

This table of results is notable for the suggestion of decreased efficacy in successive treatment sessions appearing in both the change in TWSTRS and the Pain VAS. The Patient Global Assessment is not suggestive of this, but may be the least objective in this open label study.

SAFETY RESULTS

A summary of safety results was submitted indicating percentages of subjects with reports of an adverse event within dose level groups. These analyses did not account for the number of subjects receiving multiple treatment sessions within the same dose category, so did not adequately address the number of treatments at risk of an AE to allow-quantitative comparison across dose levels. However, these analyses did not reveal any marked increase in AE rates with higher dose levels beyond that already noted for the comparison of 5000 U to 10000 U in Study 301. Absolute rates of AE incidence could also not be interpreted due to the issue of multiple treatment sessions per subject that may or may not be included within a single dose level.

Comment:

Due to the multiplicity of subjects with multiple treatment sessions within dose levels, there is no interpretable manner of presenting the totality of adverse event experience from Study 351. For purposes of labeling, reliance on the much more limited but more interpretable adverse event rates observed in Studies 301 and 302 may be preferable. Those results may also be applicable to the circumstance of a physician making an initial treatment decision for a new patient. After the patient has received several treatment sessions with BotToxB, decisions for continuation of treatment will be more dependent upon the individual patient's responses than upon labeled rates of adverse events.

Separate updates were submitted for Study 351 and for pooled results of the two uncontrolled studies (Study 352 and Study 351). A summary of the pooled results are shown in the following table for adverse events with at least a 5% incidence overall all subjects.

Table 11: Percent of Subjects Reporting Aes by Dose Group in Pooled Studies 351 and 352

Dose level	5000	10000	12500	15000	17500	20000	Any dose
actual range	>2500 U to 7500 U	7550 U to 11000 U	11500 U to <15000 U	15000 U to <17500 U	17500 U to <20000 U	=> 20000 U	12500 mdn
#subjects	n = 61	n = 445	n = 322	n = 325	n=53	n=57	n=498
# sessions	94	666	540	925	84	101	2487
Dry mouth	26	46	32	27	11	10	53
Dysphagia	15	26	25	20	11	14	38
Infection	15	10	11	17	19	14	28
Headache	13	8	6	9	9	14	18
Neck pain related to CD	3	8	8	11	11	5	18
Pain	12	5	8	7	9	5	17
Injection site pain	8	9	9	6	8	2	16
Flu syndrome	3	7	6	5	8	7	15
Dyspepsia	2	9	8	6	8	4	14
Arthralgia	7	5	9	6	2	4	14
Accidental Injury	5	5	6	6	6	4	12
Asthenia	10	5	4	3	11	9	12
Nausea	5	5	3	5	4	4	10
Pharyngitis	3	5	4	3	6	4	10
Dizziness	2	4	3	4	4	2	9
Back pain	0	2	4	6	0	0	8
Myasthenia	5	3	2	4	4	4	8
Sinusitis	0	3	5	3	4	4	8
Torticollis	2	3	2	4	8	4	7
Rash	7	3	3	2	0	2	7
Diarrhea	3	4	2	2	2	2	6
Depression	2	3	2	4	0	5	6
Parasthesia	2	2	2	5	2	0	6
Myalgia	0	2	3	2	9	0	6
Headache related to CD	3	1	4	4	0	2	6
Rhinitis	2	2	2	3	0	2	5
Bronchitis	0	2	3	2	2	2	5
Constipation	3	2	2	3	0	2	5

Only AE with at least 5% overall incidence shown
Dose level represented by median dose; which is usually 80% of actual doses
Note that subjects may be represented by more than one dose cycle within a column, and within more than one column when different doses used

Elan also submitted an update showing the distribution of maximal severity of the reported adverse events.

Table 12: Distribution of Maximal Severity of Adverse Events - Percent of Subjects Reporting Event at Specific Severity

AE	Mild	Moderate	Severe	Overall
Dry mouth	26	18	6	50
Dysphagia	23	12	3	38
Infection	16	12	1	29
Headache	11	7	2	20
Neck pain related to CD	6	10	4	20
Pain	9	8	2	19
Injection site pain	9	7	2	18
Flu Syndrome	8	8	1	17
Asthenia	9	4	1	14
Dyspepsia	7	5	2	14
Nausea	8	4	1	13
Accidental Injury	4	6	2	12
Arthralgia	5	6	1	12
Myasthenia	6	3	1	10
Pharyngitis	7	3	0	10
Back Pain	5	4	0	9
Dizziness	6	3	0	9
Sinusitis	4	4	0	8
Diarrhea	5	2	0	7
Depression	4	2	1	7
Neck pain	2	3	1	6
Myalgia	4	2	0	6
Rhinitis	4	2	0	6
Rash	5	1	0	6
Consitipation	2	3	0	5
Headache related to CD	2	3	0	5
Paresthesia	3	2	0	5
Fever	3	1	0	4
Bronchitis	1	3	0	4

All studies pooled; controlled and uncontrolled
Overall is approximate % ; = sum of rounded distributed %
Total n = 570 subjects

Comment:

Notable in this table is that most adverse events were of mild to moderate severity. This includes the most frequent adverse events.

In response to CBER request, Elan submitted an exploratory analysis of the distribution of severity of dysphagia and dry mouth by dosing group for subjects pooled from the 3 controlled studies of 009, 301, and 302.

Table 13: Percentage of Subjects with AE by Severity

	Placebo n = 104	2500 U n = 31	5000 U n = 67	10000 U n = 106
Dysphagia Mild	1	16.1	10.4	18.9
Moderate	1.9	0	0	6.6
Severe	0	0	0	0
Dry Mouth Mild	1.9	3.2	10.4	17.9
Moderate	1	0	0	13.2
Severe	0	0	1.5	2.8

Comment:

This table further suggests that AE rates are increased in an important manner with the dose of 10000 U. Both absolute frequency and distribution of severity is worsened with this dose. Dry Mouth is also higher in frequency at 5000 U than at 2500 U. This is consistent with a limitation to not recommend 10000 U as an initial starting dose. —

Absolute incidences of these two adverse events in all controlled studies pooled, with AE only within the first 4 weeks included, further suggest a dose relationship for these two AEs. Dry Mouth in the dose groups of <= 2500U, >2500 to 7500 U, and > 7500 U to 10000 U are 2%, 12%, 34%; dysphagia is 9%, 10%, 25%.

Comment:

Although this analysis is not able to provide true frequencies at each dose level due to the varying patient population included in each dose level category with variable selection of advancement of subjects from level to level, it does strongly support the expectation that adverse event rates will be increased at higher doses. This prohibits any statements in labeling or promotional materials that doses beyond 10000 U have been demonstrated as safe or well tolerated.

CLINICAL EXPERIENCE WITH NPF MANUFACTURED TOXIN

Elan stated that only Study 351 employed NPF toxin for injections. There were a total of 255 subjects who have at least 1 treatment session of exposure to NPF toxin, for a total of 338 treatment sessions. Summary analyses were submitted comparing the safety results between — and NPF produced toxin.

Table 14: Extent of Experience and Selected AE rates with — and NPF Toxin

	Dose	2500 to 7500 U	7500 to 11000 U	11000 to 15000 U	15000 to 17500 U	17500 to 20000 U	>= 20000 U	Any
—	# Subjects	49	305	198	261	29	27	413
	# Tx Sessions	74	482	342	655	40	46	1643
NPF	# Subjects	8	27	50	109	37	43	255
	# Tx Sessions	9	33	61	138	43	53	338
% Subjects with AE								
Dysphagia —		14	21	14	18	14	15	28
	NPF	25	7	6	5	5	9	7
Dry Mouth —		31	41	23	19	14	11	41
	NPF	25	7	8	7	5	9	8

Comment:

Extent of experience with NPF toxin is comparable to that of — toxin at the highest dose levels, and is a reasonable amount at the 15000 U dose level. There is limited experience with NPF toxin below 15000 U. Because there is an ordered crossover pattern (of — to NPF only) and investigators may have adjusted the injection procedure to avoid the observed sensitivities of each individual subject as subsequent sessions occurred, the AE rate comparison must be interpreted with caution. While a decrease in AE rates with NPF toxin is observed, a

practice effect cannot be distinguished from an NPF toxin related effect. Nonetheless, these data suggest there is not a NPF related increase in AE rates.

In order to avoid confounding the analysis by intermixing treatment sessions of different patients, an analysis based on same subject cohorts was requested.

Table 15: Adverse Event Rates of Same-Subject Cohorts at Crossover to NPF Toxin

		Penult	Last	First NPF	Second NPF
1 — & 1 NPF	n		250	250	
	Dysphagia		6	8	
	Dry Mouth		6	5	
1 — & 2 NPF	n		83	83	83
	Dysphagia		5	5	6
	Dry Mouth		7	8	6
2 — & 1 NPF	n	245	245	245	
	Dysphagia	7	5	5	
	Dry Mouth	11	6	7	
2 — & 2 NPF	n	83	83	83	83
	Dysphagia	7	5	5	6
	Dry Mouth	7	7	8	6

Comment:

This table is also consistent with the impression that no notable increase in AE rates occurred with the change to NPF toxin. The AE rates appear to be largely unchanged when NPF toxin was introduced. This suggests that there is no safety concern with the use of NPF toxin for commercial marketing even though only —— toxin has been well studied in controlled trials.

PEDIATRIC LABELING PROPOSAL

In response to CBER request for Elan to address the regulations for pediatric information in labeling, Elan submitted on 9/13/00 a request for waiver from obtaining data in a pediatric population.

Elan reports that published medical literature indicates prevalence of CD is approximately 3 per 10,000, or approximately 75,000 per 250 million population. Mean age of onset is reported to be early 40's, although it may range down pediatric patients. Only small minority would be below age 16; well below the 50,000 number cited in the regulations. Therefore, Elan proposes that MYOBLOC is not likely to be used by a substantial number of pediatric patients with CD. Studies of safety and effectiveness would be impractical, and a full waiver as described in 21CFR601.27©(2) is requested.

Comment:

Elan has made an adequate case that this product is unlikely to be used in substantial numbers of pediatric patients for the purpose of treatment of cervical dystonia. A pediatric waiver of studies for this indication is warranted.

GERIATRIC SUBSET ANALYSES

In response to CBER requests for subset analyses to formulate Geriatric Precautions section, Elan had stated that analyses were submitted in the previous original submission. Instead of supplying reference to that, Elan has submitted new analyses.

Efficacy

Elan submitted a table summarizing, by dose level, TWSTRS scores in pooled patients from studies 009, 301, 302.

Table 16: Efficacy in Pooled Controlled Studies by Age Subset

		Placebo	2500 U	5000 U	10000 U
Age	n	80	24	52	76
< 65 yr	Baseline	46.9	45.1	46.9	50.6
	Wk 4 Chg	3	11.4	11.2	12.9
Age	n	24	7	17	30
>= 65	Baseline	47	47.3	42.2	45.8
	Wk 4 Chg	3.8	12.6	9.3	12.5

Comment:

These data do not suggest any major differences in efficacy between the two age sets, but are too limited in number for patients over the age of 65 allow comparisons to be sensitive to even moderate differences.

Safety

Elan submitted separate tables of AE incidence in pooled studies 009, 301, 302 for subjects < age 65 and those >= age 65. These tables did not reveal any major differences in either the nature or frequency of AEs, but the numbers of subjects greater than age 65 are too limited to allow comparisons sensitive to even moderate differences.

SUMMARY

This summary pertains only to the issues that have been addressed under this supplemental review. The primary review document should be consulted for the main body of information relating to this product and the marketing application.

Updated safety and clinical performance outcome data have been submitted by Elan. There are no new safety concerns raised by the new data, but the updated data and re-focused analyses of the prior data have served to better highlight the safety concerns that do exist with this use of this product. Serious adverse events have not been observed to be associated with the use of this product. The adverse events of dysphagia and dry mouth remain the most frequent adverse events, and do appear to have impact upon the patients. Even though these events are not often severe, they nonetheless have led to discontinuation of further injections by patients.

The open label Study 352 suggests strongly that there are no benefits to dosing at levels above 10000 U in this use of BotToxB. Although this open label, known dose escalation study would have had an expectation bias of better response with the higher doses, there was no such relationship observed. Patients were not completely resolved of their symptoms on any dose, so no ceiling effect to response came into play to prevent better response. There was also no convincing evidence of a lengthened duration of response with the higher doses.

An important issue in the clinical development of this product was the change in manufacturing that occurred subsequent to the end of the phase 3 studies. A limited, but adequate amount of clinical experience was obtained with the new manufactured lots of toxin. These indicated that there was not a substantially different safety profile between the two forms of the toxin.

Dosing in the phase 3 studies appeared to be consistent in use of specific muscles and in the dose range per muscle irrespective of study or dose level. Thus, a simplified description for labeling is suitable guidance for physicians, and does bear relevance for the reported adverse event rates.

Antibody formation is seen to occur with repeated use. ELISA responses develop in a majority of patients by two years of use. Neutralizing responses develop in approximately 18% of subjects by 18 months, and appears likely to continue to increase with further usage. The clinical significance of these responses remains uncertain. There have been no demonstrated hypersensitivity responses in patients associated with these antibodies. There is a mild suggestion of lessened efficacy with antibody responses, but this remains not definitively proven. In the feasible analyses, there were no factors that could be shown to increase the propensity to develop antibodies.

RECOMMENDATION

Safety and efficacy of Botulinum Toxin Type B from Elan has been sufficiently evaluated and demonstrated. A favorable risk to benefit comparison occurs with use of the toxin in the manner described in the clinical studies. This product is recommended for marketing approval when appropriate labeling is developed.

The newer manufactured toxin (NPF toxin) appears to have a safety profile adequately represented by the overall data collected, and no special labeling comments need to be made with regard to this issue.

A phase 4 study should be conducted by Elan to improve on the understanding of the development of antibodies against the toxin over time. This should collect safety information for major safety events. However, given the present understanding of very limited risk associated with the formation of antibodies, there is not a pressing safety issue demanding that rigorous evaluation of the relationship of antibodies to efficacy be determined.